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EXAMINER

EPPERSON, JON D

ART UNIT

PAPER NUMBER

1639

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary*File Copy*

Application No.

09/679,331

Applicant(s)

DESLONGCHAMPS ET AL.

Examiner

Jon D Epperson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 10 March 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24-33 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

Please note: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1639.

Status of the Application

1. The Response filed March 10, 2003 (Paper No. 11) is acknowledged.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-10 were pending (claims 11-23 were previously withdrawn from consideration by the Examiner). Applicants cancelled claims 1-23 and added claims 24-33. Therefore, claims 24-33 are currently pending.

Change of Inventorship

4. Applicants stated, "On July 15, 2002, Applicants requested deletion of Luc Quellet and Ruoxi Lan as inventors in this application. Such deletion results from the cancellation of claims 11-23. Applicants request confirmation from the Examiner that such deletion has been made" (see Paper No. 11, page 13, paragraph 3).
5. 37 CFR 1.48(b) requires that the amendment be accompanied by:

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- (1) a request, signed by a party set forth in § 1.33(b), to correct the inventorship that identifies the named inventor or inventor's being deleted and acknowledges that the inventor's invention is no longer being claimed in the nonprovisional application; and
- (2) a fee under 37 CFR 1.17(i).

The Examiner stipulates that these two requirements have been successfully completed by Applicants (see Applicants Requests for Amendment of Inventorship (37 C.F.R. 1.48(b)) filed July 15, 2002).

Priority

6. The Examiner acknowledges the Canadian Application 2,294,459 for priority and accordingly affords Applicants their foreign priority date of **October 4, 1999**.

Withdrawn Objections/Rejections

7. The objection to claim 10 is withdrawn in view of applicant's amendments and/or arguments thereto. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

8. Claims 24-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

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skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Applicant's claim is directed to a "macrocyclic compound of the formula (I)." There are virtually an unlimited number of compounds that would fall within the scope of this claim because applicant claims not only amino acids with various side chains, but also β -amino acids, γ -amino acids, non-natural amino acids, D and L amino acids and various other spacer groups that can all be varied independently of one another to form a macrocyclic compound. Furthermore, the enormous number of chemical species that would fall within this formula are not "closely related" because the numerous substitutions that have been suggested would change the overall structure of the compounds in ways that would materially effect its form and function. For example, applicant concedes "the compounds according to the invention ... can adopt very different structures ... according to the nature of their spacer parts [and, as a result,] ... the scope of the invention is broad" (see specification page 12, paragraph 2). Furthermore, the connectivities for many of the variable substituents have not been specified (see 35 U.S.C. 112, second paragraph rejections below) and, consequently, it is not possible to determine what the full scope of the claimed invention is. As a result, applicants have not demonstrated in "full, clear, concise, and exact terms" that they are in possession of the elected invention.

With respect to adequate disclosure applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention*. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by “representative examples”) for both enablement and adequate disclosure.

Here, Applicants admit in their specification that the claims are broad and of an unpredictable nature (see specification page 12, paragraph 2). Consequently, the Examiner contends that the specification fails to provide adequate disclosure because Applicants have disclosed only a limited number of examples for tethered tripeptides that mimic RGD compounds, which would not teach a genus that would encompass virtually an unlimited number of compounds in a broad range of classes.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify all of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing examples like tethered tripeptides (see specification,

Examples) is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

The few examples provided by applicant is neither representative of the claimed genus, nor does it represent a substantial portion of the claimed genus. Furthermore, since it is not even possible to determine what the full scope of the claimed invention is (see 35 U.S.C. 112, second paragraph rejections below), applicant cannot be in possession of the full scope of the invention. Therefore, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the full scope of the claimed invention.

Response to Arguments

9. Applicant's arguments directed to the above written description rejection were considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' arguments and/or newly amended and/or newly added claims.

Applicant argues that they have narrowed their claims such that the specification as filed provides written support for the newly added and/or amended claims (see Paper No. 11 pages 14-17 wherein Applicant narrowed the claims to encompass more limited amino acid building blocks and more limited tether components).

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This is not found persuasive for the following reasons:

The Examiner contends that Applicants amendments have not gone far enough. As stated in the original rejection the “numerous substitutions that have been suggested would change the overall structure of the compounds in ways that would materially effect its form and function” and the Examiner contends that the newly amended claims would still fall within this category. Here, Applicants admit in their specification that the claims are of a broad and an unpredictable nature (see specification page 12, paragraph 2, “the compounds according to the invention ... can adopt very different structures ... according to the nature of their spacer parts [and, as a result,] ... the scope of the invention is broad”). Furthermore, Applicants have not put forth any evidence that would indicate that their amendments would alleviate this problem other than to make an unsubstantiated claim that “all of the claimed elements are related in that they utilize a multiple bond, ring or other functionality to limit conformational flexibility of the subsequent macrocyclic molecules.” Consequently, the Examiner contends that the specification fails to provide adequate disclosure because Applicants have disclosed only examples for tethered tripeptides (i.e., fall into only one class of compounds), which would not teach a genus that would encompass virtually an unlimited number of compounds in a broad range of unrelated chemical classes.

Accordingly, the rejection cited above is hereby maintained.

10. Claims 24-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for several of the tethered tripeptides that are structurally related to RGD

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that fall within the broad scope of the claimed invention (see below), is not enabling for the vast majority of compounds that fall within this broad scope. This is an enablement rejection.

Any person skilled in the art to which it pertains, or with which it is most nearly connected, would not know how to make and use the claimed invention. Applicant has not provided enough examples of how to use the claimed invention to be enabling for the full breadth of the claims. It is clear from applicant's specification how one might practice this invention with the top two compounds in claim 10 because they mimic RGD and it is clear from the specification and known in the literature that these compounds might show similar biological activity to known RGD compounds (see specification, page 11, first paragraph, which teaches a known use in the literature for RGD compounds in cell recognition). However, applicants have not provided sufficient guidance as to how to make and use any of the other compounds that might fall within the broad scope of the claimed invention, which are not related to RGD compounds.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the level of one of ordinary skill;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) Breadth of the claims and nature of the invention: Applicant concedes that the breadth of the claims is broad (see specification, page 12, second paragraph) (“the scope of the invention is broad”). Applicant’s formula (I) for a macrocyclic compound in claim 1 reads on an almost unlimited number of compounds because of the enormous number of variable groups that can be independently changed (even for the newly amended claims). For example, a variable number of amino acids, non-standard amino acids (e.g., Hyp, Orn), D and L amino acids (note that changes in stereochemistry would also lead to “structures very different from conventional β -turns”), spacer groups, all containing various R side chains (e.g., R₀, R₁, R₂, R₃, R₄, etc.) can be independently varied. Furthermore, different core structures could also be created by the different Y, L, Z and spacer groups. Furthermore, applicant concedes that these compounds would not be structurally related in form and function (see specification, page 12, second paragraph) (“the compounds ... can adopt structures very different from conventional β -turns, according to the nature of their spacer parts”). In addition, it is not possible to determine what effect these substitutions and changes in conformation will have on the therapeutic value (if any) of these macrocyclic compounds i.e., the nature of the subject matter is completely unpredictable (see Parsons et al, conclusion) (“The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study”; see also specification page 12, paragraph 2, “the compounds according to the invention ... can

adopt very different structures ... according to the nature of their spacer parts [and, as a result,] ... the scope of the invention is broad'.

(3 and 5) The state of the prior art and the level of predictability in the art: The therapeutic value for the vast majority of these macrocyclic compounds is not known in the literature. Furthermore, it would be hard to predict what biological target should be used to screen many of these compounds for biological activity and even harder to predict whether or not they would show biological activity (see Parsons et al, conclusion) ("The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study"). Even if a biological target was known, the structures of the possible variants are sufficiently diverse that one of ordinary skill would not be able to predict which compounds would be capable of binding to the given biological target (see specification page 12, paragraph 2, "the compounds according to the invention ... can adopt very different structures ... according to the nature of their spacer parts [and, as a result,] ... the scope of the invention is broad" demonstrating the unpredictable nature of the claimed invention because it reads on many "unrelated" i.e., very different structures). Therefore, the state of the prior art and the level of predictability in the art is quite low.

(4) The level of one of ordinary skill: The level of skill would be high, a person would most likely require a Ph.D. level degree.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have not provided any examples for the vast majority of

compounds that fall within the scope of these broad claims which show their usefulness. Therefore, one of skill in the art would not know how to make and use the claimed invention (with the exception of the RGD analogs as mentioned above). Furthermore, there is no generic strategy for determining what effect these substitutions and resulting conformational changes will have on the binding affinity and/or selectivity (note: in paper 11, Applicants make only an unsubstantiated claim that all of the newly amended claimed elements would “limit conformational flexibility” presumably to somehow overcome this rejection). In addition, there is no “core” structure from which a biological entity might bind to. The only constant “core” structure given by general formula (I) is an amide bond and, as a result, there can be no common structural motif to which a biological ligand of interest would bind.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The instant specification for all the reasons asserted above does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using the full scope of the claimed compounds. For example, it is not clear what immediate value a compound of formula (I) would have to the public when the (A) part represents a γ -amino acid with a methyl side chain, the (B) part represents a β -amino acid with an aromatic ether side chain, (c) represents a D-amino acid with a methionine side chain, the tether portion is $-\text{CH}_2-\text{S}-\text{CH}_2-$ and the “constant region” is a glycine radical. It would take undue experimentation to determine this value because as applicant concedes the “compounds according to the invention have much flexibility and can adopt structures

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very different from conventional β -turns, according to the nature of their spacer parts.”

Furthermore, applicant concedes that the vast majority of these compounds are only “potentially” useful in a research setting (see specification, page 19, second paragraph) (“Among the potential uses of the compounds according the present invention are uses in scientific research as research reagents”) and only provides a long “non-specific” list of potential diseases where these macrocyclic compounds “might” some day be useful (see pages 18-19 showing a long non-specific list of potential diseases). Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention **as broadly as it is claimed**. See also *Brenner v. Manson*, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting that “a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.”).

Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Response to Arguments

11. Applicant’s arguments directed to the above Enablement rejection were considered but were not deemed persuasive for the following reasons. Please note that the above rejection has

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been modified from its original version to more clearly address applicants' arguments and/or newly amended and/or newly added claims.

Applicant argues that they have narrowed their claims such that the specification as filed provides Enablement for the newly added and/or amended claims (see Paper No. 11 page 17).

This is not found persuasive for the following reasons:

As an initial matter it is noted that Applicants have not explicitly addressed the majority of Wands factors that were set forth by the Examiner in the previous Office Action and, as a result, the Examiner maintains that each one of the Wands factors addressed above is still applicable to the newly amended claims. Furthermore, the Examiner contends that Applicants newly amended claims are still broad and of an unpredictable nature as set forth in Wands factors (1-2) (see above rejection). The newly amended claims would still encompass an almost unlimited number of chemical unrelated compounds. Furthermore, Applicants have not set forth any evidence refuting the Examiner's position that Applicants broad scope would also be of "unpredictable" nature (see specification page 12, paragraph 2, "the compounds according to the invention ... can adopt very different structures ... according to the nature of their spacer parts [and, as a result,] ... the scope of the invention is broad"). Furthermore, Applicants have not put forth any evidence that would indicate that their amendments would alleviate this problem other than to make an unsubstantiated claim that "all of the [newly] claimed elements are related in that they utilize a multiple bond, ring or other functionality to limit conformational flexibility of the subsequent macrocyclic molecules." This statement is not afforded any weight because there is no data to back it up and said elements still read on an almost unlimited number of possibilities (e.g., the phrase "or other functionality" is open ended and does not place any practical

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limitations on the claim). Furthermore, Applicants did not refute Wands factors (3-7) above and, as a result, the Examiner holds this to be an implicit concession on the part of Applicants.

Finally, Applicants state that “one skilled in the art would be able to use the compound of the present invention with known screening methods such as biological high throughput screening assays, and radioassays to identify compounds having antibacterial, antifungal, antiviral, antineoplastic or other pharmaceutical biological or chemical activity” to presumably refute Wands factor (8). As an initial matter, the Examiner notes that no “specific” utilities are being disclosed for any of these “testable” compounds other than a mere laundry list of potential activities. Furthermore, it is noted that merely disclosing the ability to make a compound or compounds (e.g. a library) is in itself insufficient utility to satisfy 35 USC 112, first paragraph as determined by the U.S. Supreme Court. . Eg. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966). Finally, the majority of claimed compounds are not recognizable as analogous to compounds with a recognized pharmacological (i.e., RGD compounds) activity. Consequently, a person of skill in the art would not know what activity to screen for from the large laundry list of potential diseases and/or other biological activities. Therefore, the Examiner maintains that an undue amount of experimentation would be required i.e., someone else (other than applicant) would have to discover what the vast majority of these claimed compounds would be useful for which clearly represents only an invitation to experiment. See *Brenner v. Manson* cited above.

Consequently, the Examiner contends that the specification fails to provide adequate disclosure because Applicants have disclosed only examples for tethered tripeptides (i.e., RGD mimics), which would not teach a genus that would encompass virtually an unlimited number of compounds in a broad range of unrelated chemical classes that have unknown functions.

Accordingly, the rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 112, second paragraph

12. Claims 24-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Withdrawn.

B. In claim 24, the side chains of the macrocyclic ring represented by formula (I) are vague and indefinite because it is not clear what structures many of these side chains represent and it is also not clear how (at what position) many of the side chain groups are covalently attached to the macro cycle. For example, applicant shows R₀, R₁, R₂, R₃ and R₄ to be independently selected from a large group (see paper 11, page 5) wherein one of the members can be a pyrrolidine substituted with either a carboxylic acid at the 2 position or a hydroxy and a carboxylic acid at the 4 and 2 positions, respectively. These compounds and many others do not have horizontal lines indicating the point of attachment and, as a result, it is not clear where the substitution would occur. Applicants are requested to clarify and/or correct. Therefore, claim 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

C. In claim 24, the internal groups of the bivalent L, A and B are vague and indefinite because it is not clear what structures A and B represent and it is also not clear how (at what position) many of the A and B groups are covalently attached to the L

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bivalent radical. For example, applicant shows A and B to be independently selected from a large group (page 49) wherein one of the members can be an $-\text{SO}_2\text{-NH}$ (see paper 11, page 6). It is not clear where the second bond forms i.e., there is only one attachment site shown at the S. Does applicant mean that this bivalent radical has only one attachment site? Does it mean that both attachment sites are at the S or one at the S and O or S and N. Applicants are requested to clarify and/or correct for all ambiguous groups. Therefore, claim 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

D. Withdrawn.

E. Withdrawn.

Response

13. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejections were considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

A. Withdrawn.

B. Applicants argue that "Applicants have corrected the missing bonds in the claims and in the specification."

This is not found persuasive for the following reasons:

The Examiner contends that Applicants statements and amendments simply do not address all of the issues set forth in section B (see above newly amended rejection for examples).

C. Applicants argue that “Applicants have corrected the missing bonds in the claims and in the specification.”

This is not found persuasive for the following reasons:

The Examiner contends that Applicants statements and amendments simply do not address all of the issues set forth in section C (see above newly amended rejection for examples).

D. Withdrawn.

E. Withdrawn.

Accordingly, the 35 U.S.C. 112, second paragraph rejections cited above (i.e., B-C) are hereby maintained.

New Rejections and Objections

Objections to the Claims

14. Claim(s) 24-33 are objected to because of the following informalities:

A. Claim 24-33 are missing a period at the end of the claim (please note that there is now a “- -” mark at the end of each claim. Appropriate correction is required.

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- B. Claim 27 recites "same meanings as give in" wherein it should read "same meaning as given in" i.e., the "n" is missing. Appropriate correction is required.

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 24-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (New Matter).

New **claim 24** recites for the R_0 , R_1 , R_2 , R_3 and R_4 groups " $-\text{CH}_2$ ", " CH_2 " and $-\text{CHO}$ for R_5 . The Examiner cannot find support for these new limitations. Furthermore, the claim goes on to recite that for "L" i.e., $-(\text{CH}_2)_d\text{-A-(CH}_2)_j\text{-B-(CH}_2)_e$ - that "d" can be "an integer from 0 to 5." The Examiner only finds support for "d" that is an integer from "1" to 5 as in the original claim i.e., the Examiner cannot find support for the "0" limitation. In addition, the claim goes on to recite "when j is 0, A and/or B is present." The Examiner only finds support when "A or B" is present i.e., the Examiner cannot find support for the "and/or" limitation. Furthermore, the claim recites new chemical groups for A and B including new six member aromatic rings and aromatic rings with "Na" substituted within the ring (see 35 U.S.C. 112, second paragraph rejection below) that the Examiner cannot find support for. Furthermore, the claim recites limitation

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wherein R is defined as being a -CH=CH- in the “Z or E” configuration wherein the original claim only had the -CH=CH- in the “Z” configuration only. Finally, the Examiner cannot find support wherein the G group is defined as a “covalent bond.” If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found i.e., Applicant must point to a specific “line” within the patent for “each” limitation stated above. Therefore, claim 24 and all dependent claims are rejected under 35 U.S.C. 112, first paragraph for containing New Matter.

For *claims 25, 27, 28 and 30*, to the extent that the phrase “protective groups for orthogonal protections” extends beyond “protective groups commonly used for orthogonal protections” (i.e., to the extent that the deletion of the word “commonly” increases the breadth of the claim), the increased breadth constitutes new matter, since there is no specification support or original claim support for such scope; nor has applicant provided any indication where such support exists. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found i.e., Applicant must point to a specific “line” within the patent for the limitation stated above. Therefore, claims 25, 27, 28 and 30 and all dependent claims are rejected under 35 U.S.C. 112, first paragraph for containing New Matter.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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16. Claims 24-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claim 24** recites the limitation wherein R_0 , R_1 , R_2 , R_3 and R_4 are “-CH₂”, “CH₂”, “-CH₂ CH₂~CO₂H” “- CH₂ CH₂C(=O)NH₂”, etc. wherein many of the bonds are missing and/or are not described using standard nomenclature i.e., the “~” bond, for example.

Furthermore, it is not clear how the “-CH₂” differs from the “CH₂” and whether Applicant intends this to stand-alone i.e., as a radical or be apart of some other covalent system. Applicants are requested to clarify. Furthermore, the Examiner respectfully asks Applicants to double check the entire claim for other potential typographical errors.

Therefore, claim 24 and all dependent claims are rejected under 35 USC 112, second paragraph.

B. **Claim 24** recited a six-member ring with a “Na” at one of the vertices. The Examiner believes that Applicants intended “N” not “Na”. Applicants are requested to clarify and/or correct. Therefore, claim 24 and all dependent claims are rejected under 35 USC 112, second paragraph.

C. **Claim 25** recites “G₁P” instead of “PG₁” in compound (9). Applicants are requested to clarify and/or correct only “PG₁” is defined in the claim. Therefore, claim 24 and all dependent claims are rejected under 35 USC 112, second paragraph.

D. **Claim 26** recites R_1 , but no R_1 group is shown in compound (9) (note that the compound now recites two “R₂” groups). Applicants are requested to clarify and/or

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correct. Therefore, claim 26 and all dependent claims are rejected under 35 USC 112, second paragraph.

E. For *claims 28-29*, compounds (11-12) recite the group "X", but do not define what the group is. Applicants are requested to clarify and/or correct. Therefore claim 28 and all dependent claims are rejected under 35 USC 112, second paragraph.

F. For *claims 32-33*, several of the bonds in the compounds listed are not connected to an atom (e.g., there are several examples but see the imidazole ring in the last compound). Furthermore, many of the compounds use the term "NH_a" wherein it is not clear what the "a" stands for. Applicants are requested to clarify and/or correct.

Therefore, claims 32-33 and all dependent claims are rejected under 35 USC 112, second paragraph.

G. For *claim 33*, it is not clear what the purpose of the "arrow" stands for i.e., how does the arrow differ from the "-" bond? Applicants are requested to clarify and/or correct. Therefore claim 33 is rejected under 35 USC 112, second paragraph.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

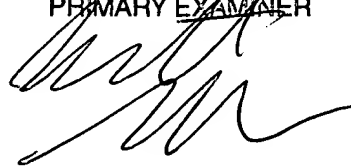
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D. Epperson, Ph.D. whose telephone number is (703) 308-2423. The examiner can normally be reached on Monday-Thursday from 9:30 to 7:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon D. Epperson, Ph.D.
May 27, 2003

BENNETT CELSA
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Bennett Celsa', is written over the printed name and title.